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Experiences with Commercial Production Scale Operation of Dissolving Metal Reduction Using Lithium Metal and Liquid Ammonia

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Abstract:

The final step which generates free base in the synthesis of Sumanirole Maleate (PNU-95666E) consists of a cryogenic dissolving metal reduction using lithium metal and liquid ammonia. This chemistry was new to the Pfizer API production plant. Due to the hazards associated with the handling of lithium metal and ammonia gas at cryogenic reaction temperature, special challenges were encountered related to the design of the equipment, choice and handling of materials, operations, waste treatment, and both safety and economic issues. The topics discussed in this article include the use of Li instead of Na or K, impact of the choice of physical form of lithium metal, design of the lithium addition apparatus, and problems experienced during the addition. We also discuss techniques for addition of ammonia to the reactor, evaporation of ammonia from the reaction mixture, options for ammonia disposal, and internal reuse of ammonia. Comments on hazards for this reaction are also provided. It is hoped that this document will be of benefit to other professionals who may want to develop and scale-up dissolving metal reduction processes.

Introduction

Sumanirole Maleate (PNU-95666E) was a drug candidate developed by Pharmacia & Upjohn (now Pfizer). The route for synthesis of PNU-95666E has been described elsewhere[1−5] and includes a dissolving metal reduction[6,7] to convert the aziridine intermediate (**1**) to the free base of the API. This reaction is shown in Scheme 1.

The dissolving metal reduction, which is carried out by dissolving the aziridine intermediate and lithium metal in refluxing liquid ammonia at −33 °C, poses challenges in handling these materials safely. We have carried out more than 15 runs at commercial manufacturing scale in two different API production facilities to generate supplies for Phase III clinical trials. The dissolving metal reduction was not previously run routinely in our production plants. This paper discusses our experience with running large scale dissolving metal reductions and the challenges of handling the highly reactive lithium metal and liquid ammonia, low reaction temperatures, and waste disposal. During our large-scale operation, we considered various alternatives regarding different physical forms of lithium metal, handling of lithium and ammonia, waste disposal, safety of operation, etc. The lessons learned and know-how generated during this large scale dissolving metal reduction operation are summarized in this paper. It is hoped that this information will be beneficial to other personnel in process R&D/production who may need to work with dissolving metal reductions.

Results and Discussion

Brief Description of Process and Equipment. A mixture of the aziridine intermediate (**1**), *tert*-amyl alcohol, and anhydrous ammonia is cooled to −33 °C. Lithium metal is then added in portions due to the exothermicity of the reaction. After the reduction is complete, the reaction mixture changes from a gray-yellow slurry to a dark blue mixture. This dark blue reaction mixture is stirred for about an hour to ensure that the dark blue color persists. Then excess lithium is quenched with water, which is also added in portions. After the quench is complete, the reaction mixture changes color from dark blue to gray. The ammonia solution is allowed to evaporate to dryness, and the ammonia distillate is recovered in the receiver for use in the subsequent lot. The dry residue is further processed in the next step of the synthesis. Any residual ammonia is removed by dissolution in methanol followed by solvent exchanges.

The production scale reaction was conducted using a 6000 L glass-lined vessel. The receiver was a 4000 L glass-lined vessel, and the condenser was Monel. Selection of the vessels was based on availability of equipment in the multipurpose production plant. Both vessels and condenser can be cooled to −40 °C using Syltherm. A special lithium shot loader was added as described later in this report. Ammonia was added from 150 lb cylinders. For a 50 kg aziridine batch size, the actual process volume in the tank was about 2500 L, but the batch size can be increased further using the existing equipment. In our production runs, the batch size was limited to 50 kg because of the need to limit the batch value at risk.

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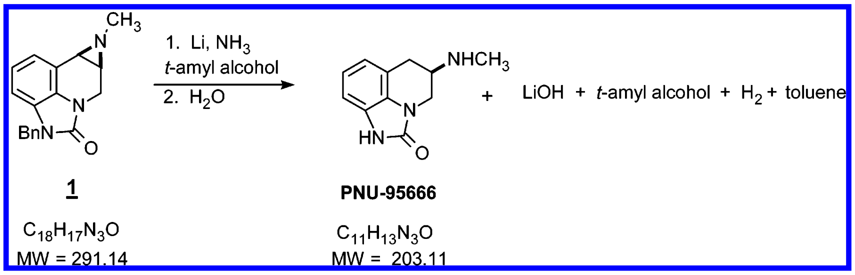
Scheme 1



For the 50 kg aziridine (**1**) batch size, the amount of *tert*-amyl alcohol used as the proton source was 53 kg/lot (3.5 mol/mol of aziridine) with liquid ammonia used as the solvent (1500 kg or 2500 L). Lithium (6.2 kg, i.e., 5.2 mol/mol of aziridine) was added in shots of 100 or 200 g. The reaction temperature was −33 °C, the boiling point of ammonia. Running the reaction at the boiling point of ammonia simplifies temperature control. The degree of cooling available to the reactor influences the temperature chosen to run the reaction. Since the reaction vessel in our plant had good cooling, it could have allowed running the reaction at even lower temperatures. For facilities where cooling in the reactor is not as good, it is possible to run the reaction at a temperature higher than the normal boiling point of ammonia by running under pressure. Clearly in that case, the ability of the vessel to withstand pressure and an increase in the potential for ammonia leaks from fittings etc, need to be considered. It is also necessary to evaluate the impact of the reaction temperature on the byproducts and speed of the reaction. In our case, the reaction end-point was determined by observing a color change during reaction. The color of the reaction mixture was normally yellow-gray and it became deep blue when excess Li was present. Considering the hazardous nature of the reaction mixture and sampling difficulties, calling the reaction end point by color change was very convenient in the production environment.

When complete, the reaction was quenched by adding 10 L of water (3.26 mol of water/mol of aziridine) in portions of 1 L over about half an hour, which easily controlled the exotherm. The quench end point was also determined by color change. When there was no excess lithium present, the reaction mixture color changed from deep blue back to yellow-gray.

Hazards Associated with Lithium Metal and Ammonia. Lithium metal reacts violently with water to give off flammable explosive hydrogen gas. Lithium metal can react with air to form lithium oxide, with nitrogen to form lithium nitride and with ammonia to form lithium amide. Once the lithium container is opened, unused lithium should be stored in mineral oil or under argon. Solid lithium metal may cause skin and eye burns, as lithium reacts with moisture to form corrosive LiOH. When fighting lithium fires, use of dry graphite powder or dry lithium chloride is recommended and water, sand, carbon dioxide, dry chemical, or halon should not be used.

Ammonia is highly corrosive and irritating to the skin, eyes, and respiratory system. The boiling point of liquid ammonia is −33 °C, and very cold temperatures are needed when it is used as a reaction solvent. If the temperature increases during reaction or if cooling fails, there is the risk of overpressurization in the vessel. It is essential to eliminate all leaks, provide good ventilation, and install suitable ammonia alarms near the equipment handling ammonia.

Comments on Use of Lithium Metal instead of Na or K in Reductions. Lithium, sodium, and potassium show similar properties for reductions in liquid ammonia. However, there are certain advantages to using lithium metal as described in the literature.[8] These advantages are summarized below. Lithium has a higher molar solubility in liquid ammonia, and a higher reduction potential than sodium and potassium. At −33 °C, the solubilities expressed in g of atoms of metal/mol of ammonia are 0.26 for Li, 0.18 for Na, and 0.21 for K. This permits the use of larger quantities of cosolvents, which improves the solubility of high-molecular-weight compounds that tend to be less soluble in liquid ammonia. Another advantage is that the higher reduction rate obtained with lithium minimizes unfavorable side reactions. The relative reaction rate for benzene reduction has been reported as 250 for Li, 4 for sodium, and 1 for potassium.[8] Another advantage of lithium metal is that during dissolving metal reductions, alcohols such as amyl alcohol or *tert*-butyl alcohol are needed as strong proton donors. Trace amounts of transition metal may enter the reaction with the liquid ammonia, as trace contaminants in the alkali metal or due to slight abrasions in the metallic equipment. It has been demonstrated that the detrimental side reaction of alkali metals with the alcohol proton donor is strongly catalyzed by trace amounts of various transition metals, particularly iron. When using lithium, this side reaction is almost negligible. Lithium is also considerably less pyrophoric and safer to use than sodium and potassium metal.

Choice of Physical Form of Lithium Metal. Lithium metal for commercial use is available from suppliers such as FMC, Chemetall, and Postin Products. These suppliers sell lithium in a variety of physical forms, which impact handling, setup, and process, vide infra.

(a) Lithium in mineral oil or vaseline. This is a mixture containing about 30 wt % lithium. Handling of lithium in this form is rather messy and cumbersome. It is also necessary to remove the mineral oil from the final product by extractions.

(b) Lithium powder. This is a fine powder about 50 microns in size. The surface area is very large, and there is a much greater hazard potential due to the increased activity. Physical handling of fine powder is also problematic with

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(8) "Lithium Metal − Properties and Applications" Product Brochure from Chemetall GMBH, Lithium Division, Frankfurt, Germany.

the possibility of physical loss and a greater risk of plugging up valves, lines, etc.

(c) Lithium granulates. These are larger size particles (2.5 mm diameter) and are easier to handle. They have a significantly lower surface area compared to the powder and are safer.

(d) Lithium sand with passivated coating. When lithium sand (0.6 mm) is allowed to react with pressurized carbon dioxide it forms a passivating coating of lithium carbonate. This coated lithium sand is dry and stable when exposed to air. The surface area of coated sand is intermediate between powder and lithium rods. Although lithium sand is easier to handle than lithium powder or lithium suspension in mineral oil, in our hands, the sand tended to plug up valves in the lithium shot loader. The lithium carbonate coating reacts with the ammonia solvent to give insoluble ammonium carbonate in the reaction mixture. These solids interfere with agitation at high concentrations, and it was necessary to increase the amount of ammonia solvent when the coated lithium sand was used.

(e) Lithium rods: These are available in sizes typically 10 to 20 mm in diameter and up to 250 mm long. They are available in many different sizes and shapes (rectangular or circular cross section). They can also be custom-made. Depending on dimensions chosen, lithium rods are easy to handle.

(f) Lithium blocks or cones: These are typically much larger in size, up to 1800 g each. They were too large for our application.

Lithium rods, sand, and powder are available in sealed pouches made of aluminum or tin foil packed under inert argon gas. The pouches should be opened just before use. The empty pouches need to be collected and deactivated after use by immersing them in water or alcohol, which deactivates any residuals.

Lithium exposed to air loses activity due to reaction with moisture, air, and nitrogen resulting in the formation of lithium hydroxide/nitride. Passivated lithium sand coated with carbonate is stable to air and moisture for short periods, but when kept exposed for several months, it loses activity by forming lithium hydroxide.

Some suppliers sell lithium rods in technical grade as well as battery grade. We used the battery grade lithium even though it is more expensive. The supplier indicated that the technical grade lithium allows a higher level of sodium impurity. Second, during machining of these lithium rods, there is a small amount of some residual oil on the surface of the lithium rods. In preparation of the battery grade lithium rods, this residual oil is washed off using a solvent and the rods are dried. In preparation of the technical grade lithium, this residual oil remains. Since the process used for Sumanirole Maleate does not have an extraction step after the dissolving metal reduction, this oil could be carried into the final product. Also, with this step close to the final API step, use of technical grade lithium would require development of an assay for the residual oil level in the final product and a specification for the oil content. It was much simpler to use the battery grade lithium and have the oil removed before using the lithium in the process. Even though the battery grade lithium is more costly than technical grade lithium, lithium itself is a very small fraction of the total cost of raw materials needed to make Sumanirole Maleate.

In our early production runs, lithium sand (0.6 mm diameter) was used. Due to operational problems associated with lithium sand, however, we switched to cylindrical lithium rods (100 g each, 1.5 in. diameter × 6.5 in. length). From considerations of safety and ease of handling in the production plant, these lithium rods were found to be superior.

Lithium Addition Apparatus. The final design of the apparatus used for adding lithium rods is shown in Figure 1. It was developed after our experience with lithium sand and after discussions with both suppliers of lithium and contract manufacturers with experience in running dissolving metal reductions.

The basic setup consists of two full port 4” SS316 ball valves (Jamesbury) with Teflon seats and a 12” long spool piece between the valves made of 3” diameter polished SS316 pipe. These valve opening and pipe diameter sizes ensure that lithium will be free flowing. A nitrogen purge line is connected to the spool piece. Alternatively this line can be connected to a vacuum line. The bottom valve is flanged directly to the reactor. There is a blind flange on the top valve to keep out particulates between runs. The two valves in the apparatus are manually operated. Care is taken to make sure that only one valve is open at a time to avoid ammonia leaking into the operating area. When this process was transferred to the second production facility, automated valves were used with an interlock to avoid opening of both valves at the same time. However the automated valves require a longer time between additions of lithium rods. The apparatus is located on the reactor away from the condenser line to minimize exposure to ammonia vapors thus reducing the risk of the exothermic lithium amide formation in the shot loader.

The density of lithium metal is 0.53 g/mL, and the density of liquid ammonia is 0.7 g/mL, so lithium metal floats on the liquid ammonia and there is no damage to the glass lining of the vessel. The rods dissolved quickly in ammonia (1 to 2 min). The position of the rod and degree of dissolution could be monitored by watching the blue streak on the surface of the liquid as the rod dissolves. The typical total addition time for the lithium rods for a production run was about 2 h. A longer time was required with lithium sand due to problems with flowability and valve plugging. Before adding the next lithium shot, we waited for dissolution of the previous lithium shot by watching the surface of the liquid and monitoring both pressure buildup and foaming. We did not experience any significant problem with pressure buildup in our operation. Foaming, which was a significant problem with lithium sand, was not a problem with lithium rods. Since the reaction was carried out at the boiling point of ammonia, we did not see a temperature increase during lithium addition.

Lessons Learned from Use of Coated Lithium Sand in Early Production Runs. The lessons learned from use

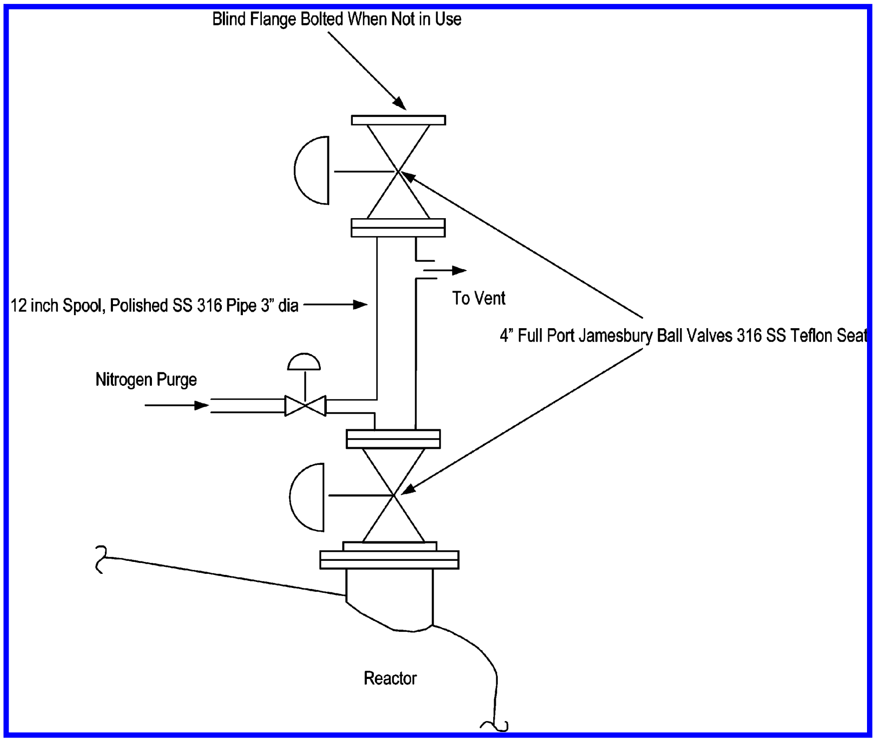

Figure 1. **Schematic diagram for the lithium charging apparatus.**

of coated lithium sand in early production runs are summarized as follows.

(a) Flowability of lithium sand can cause difficulties if the addition apparatus is not properly designed.

(b) Avoid locating the lithium add funnel where the lithium may see excessive ammonia vapors and result in exothermic lithium amide formation.

(c) Valve openings and valve design should be such that hang-up of lithium sand is avoided.

(d) Gear-operated valves are contraindicated, as they take a longer time to open and close. This results in loss of nitrogen pressure on the charge funnel, slows lithium sand addition rate, and allows ammonia vapors to react with both the passivating carbonate coating on lithium sand and lithium itself.

(e) Use separate ports for lithium addition and water addition. Visual examination cannot ascertain the absence of lithium sand/dust left in valves or addition funnels.

(f) Use small shots of lithium. Adding large amounts of lithium sand in the add funnel at a time can plug up the valves and cause problems.

(g) After each lithium shot is added, visually inspect to ensure that the spool piece is clear.

(h) Make sure that ammonia vapors in the add funnel piping are purged with nitrogen or removed using vacuum between consecutive lithium shot additions.

(i) Running the reaction at the boiling point of ammonia makes temperature control easy but can increase potential ammonia vapor exposure to operators. It also increases the chances of lithium amide formation during lithium addition which may damage plastic valve seats due to heat generation.

(j) Process and equipment configuration should allow easy access to the lithium addition funnel. Appropriate ventilation, alarms, personal protection, and fire extinguishers should be readily available.

(k) Take precautions to address the possibility of dropping lithium outside the addition apparatus.

(l) Use automation to safeguard that both valves (top and bottom) are not open at the same time to avoid exposure to ammonia.

Deterioration of Lithium Sand on Storage. Laboratory evaluations were conducted on an old lot of lithium sand that had been removed from the sealed pouch about two years prior. It appeared that the passivating coating had deteriorated after this storage and the lithium requirement in these runs was between 2 and 3 times the normal lithium requirement resulting in a lower yield. When these runs were repeated using a newly opened pouch of lithium sand, the lithium requirement and yields were back to normal. Thus the passivating coating on the lithium sand does not completely protect lithium from the effects of air and moisture in air over prolonged storage.

Addition of Ammonia to the Reactor. The following comments describe the techniques and precautions to be taken when charging ammonia to the reactor.

Fresh ammonia was added to the reactor from a 150 lb ammonia cylinder manifold located outside the cubicle with deadhead vacuum applied to the reactor. Three cylinders placed on a floor scale were charged one at a time. A fan was placed next to the floor scale to disperse any ammonia vapor.

The bottom valves for the reactor and receiver were changed from angle valves to ball valves due to the tendency of angle valves to leak at extremely cold temperatures. An ammonia detection system with alarms in the cubicle and hallway was installed. Scott Air Packs were used for personal protection. Before beginning the charge, the reactor was set for reflux with condenser and jacket set for LT −40 °C. The pot temperature was maintained below −35 °C during addition. Leak tests were done before starting the ammonia add, and any leaks were fixed.

We also explored the possibility of obtaining ammonia from an onsite tank trailer provided by the ammonia supplier instead of using ammonia cylinders. While the ammonia supplier would provide the supply tank trailer, significant capital would be needed to use such a tank for supplying ammonia to the reactor. For instance, a new ammonia pump, instrumentation for operator safety, thermal oxidizer protection, micromotion flow measurement, and structural/civil engineering modifications would be required. Due to this capital expense for a potentially temporary operation, we decided to use ammonia cylinders instead. While ammonia cylinders are available at larger sizes as well, we chose 150 lb cylinders due to the ease of handling.

Evaporation of Ammonia from Reaction Mixture. After quenching the reaction, the liquid ammonia solvent was removed from the reaction mixture as follows. To avoid overpressurization during evaporation, the jacket temperature in the reactor was increased gradually. The ammonia vapors were condensed in the receiver vessel for reuse or disposal by maintaining the condenser and receiver at −40 °C. The reactor jacket temperature was slowly increased from −35 °C to 27 °C (not allowed to exceed 30 °C), and the pot temperature increased from −35 °C to about 5 °C. The jacket temperature was adjusted to maintain the pot pressure below 5 psig. A log of hourly readings of the pot pressure, jacket temp, and pot and receiver temp and volumes was maintained. If the pressure exceeded 5 psig, the jacket temperature was lowered. The complete evaporation of the ammonia took about 24 h. When finished, the pot volume was about 150−175 L, a nearly dry paste/slurry was observed and no more ammonia was condensing in the receiver, but a small amount of ammonia still remained in the solids in the vessel. This residual ammonia was completely removed during the workup by dissolving the solids in methanol and carrying out methanol solvent exchanges. More than 95% of the ammonia used was recovered in the receiver and kept at −40 °C until ready to use in the next run with a small makeup with fresh ammonia.

Disposal of Ammonia Evaporated from Reaction Mixture. Disposal of ammonia evaporated from the reaction mixture posed a significant challenge. Several potential options were evaluated with the help of the environmental health and safety group.

(1) Internal reuse of recovered ammonia in the subsequent lot: This was the most desirable alternative since it greatly reduces the ammonia waste. Only the recovered ammonia from the last lot of the campaign would have to be disposed of. This option reduces the total cost of purchased ammonia as well the volume of waste ammonia and cost of disposal of the waste ammonia. However, using this option requires additional process R&D studies to demonstrate that there is no significant buildup of impurities in the ammonia on recycle and that the product quality does not suffer.

(2) Recycle of the recovered ammonia back to the supplier or another off-site processor: This is the next preferred solution if reuse of ammonia in the next run poses quality problems. The recovered ammonia can be sold to an off-site supplier who sells it for agricultural fertilizer use as long as it does not contain organic solvents. This option reduces the waste disposal cost but not the waste volume.

(3) Discharge of the ammonia to the sanitary sewer as aqueous ammonium hydroxide or ammonium sulfate waste: In our case, this option would have doubled the ammonia concentration in the stream received by the city water treatment plant. This significant change would have required advance piloting by the water treatment plant to test its suitability. In addition, the exit stream would have to be pH adjusted and bled into the sewer over a period of time determined by the water treatment plant.

(4) Off-site treatment: The ammonia gas from evaporation may be scrubbed in an aqueous solution or water may be added to the condensed liquid ammonia. The resulting aqueous ammonia solution (about 2000 gallon/lot) may be shipped off-site for treatment (biological, chemical, or thermal destruction) or for use as a fertilizer. This method may require storage of the aqueous ammonia waste on-site and would result in added costs for treatment off-site.

(5) Thermal oxidation: The ammonia vapors may be combusted in a thermal oxidizer unit. However, depending on the threshold limits for Nox emissions, additional permits from the appropriate environmental regulatory agency may be required. Permitting is a lengthy process taking years and requiring a public comment period.

Based on this analysis, we decided to explore the possibility of internal reuse of ammonia recovered during evaporation of the reaction mixture. Additional laboratory work was conducted to demonstrate the feasibility of reusing the ammonia in the next step.

Recycle and Internal Reuse of Ammonia. Recycle of liquid ammonia distillate in the next lot was the best option from the considerations of green chemistry, environmental regulations, process economics, and capital needs. The recycle and reuse of ammonia would minimize the ammonia waste generated and reduce the consumption of ammonia and cost of waste disposal. It would also minimize capital needs for storing ammonia distillate or aqueous ammonia waste and minimize the cost associated with a two-shift dissolving/neutralizing ammonia operation.

Laboratory work to demonstrate that ammonia distillate can be recycled and reused was carried out in our process R&D labs. We carried out laboratory runs without ammonia recycle and with ammonia recycle in multicycle experiments. The recovery of ammonia is affected by the cooling available and leaks in the apparatus. We were able to recover more than 95% of the ammonia in the production plant compared to only 55 to 60% in laboratory runs. The acceptability of the recycled ammonia was determined based on potency of recovered ammonia in multicycle runs to determine if small impurity levels build up. Since a large and representative sample would be necessary, it was decided to carry out these determinations using samples from production plant runs.

Sample bombs (1 L capacity) were ordered from the ammonia supplier. The liquid ammonia was sampled by precooling the sample bomb in dry ice and filling it with the recycled ammonia while making sure that ammonia liquid (not gas) was going into the bomb. Samples of the ammonia distillate after 5 recycles were assayed as 101% ammonia by titration, 0.08 wt % *tert*-amyl alcohol, 0.08 wt % toluene, and LT 50 ppm (assay limit) water. Thus the quality of recycled ammonia was quite good after a multicycle operation. In the next production campaign, results indicated that the potencies of ammonia distillate were good and did not decrease from lot to lot despite recycling and reusing ammonia. No impact on the product quality, yield, or processing was observed as a result of recycling and reusing the ammonia. Thus recycle and reuse of ammonia were shown to be acceptable.

Hazard Evaluations. The process safety laboratory carried out reaction calorimeter experiments to determine the heat of reaction and adiabatic temperature rise on addition of lithium sand during the dissolving metal reduction. Conditions for the reaction calorimeter run were as follows: pot temp −50 °C, no reflux, lithium shot size corresponding to a 0.5 kg lithium shot for a 50 kg batch. The total heat of reaction due to addition of all lithium was measured to be −46.3 kcal/mol of lithium and represented an adiabatic temp rise of 26.6 °C. Heat of reaction during the water quench was measured to be −8.4 kcal/mol of water representing a 3.9 °C adiabatic temp rise. The heat of reaction of dissolving the liquid ammonia in water to make 22% ammonia solution for disposal at the end of the campaign was calculated to be −16.1 kcal/mol of ammonia. This would require a controlled addition rate lasting more than 10 h in the production plant. If the dissolving metal reduction is carried out at the boiling point of ammonia (−33 °C), the heat of reaction will cause evaporation of ammonia rather than a temperature rise. Calculations by the process safety laboratory indicate that, on addition of 0.5 kg lithium shot, 12.1 kg of ammonia would be evaporated from the reactor. If the water used for the reaction quench is added over 30 min, ammonia is evaporated at a rate of 6.1 kg/h. There was adequate headspace in the reactor to handle this load.

A hazardous operation review for the dissolving metal reduction was conducted before initiating production runs. The issues considered when finalizing the process included: the potential for a lithium rod to hang-up in the spool piece, repetitive charging operation for the lithium rods, nitrogen purge during each lithium rod charge, top and bottom valve sequence of operation, ergonomic issues, potential for ammonia vapors leaking past the bottom valve and reacting with residual lithium in the spool piece, available ventilation for spool piece venting, operator personal protective equipment during charging, visual inspection of the spool piece after each charge, spool piece cleaning at the end of the run, addition of lithium rods too quickly while reactor contents are refluxing, safeguards in the event of a dropped lithium rod, lithium rod packaging waste disposal, and fire protection near the equipment.

Conclusions

The synthesis of Sumanirole Maleate (PNU-95666E) consists of a dissolving metal reduction step using lithium metal and liquid ammonia, a new chemistry for the Pfizer production plants. Special challenges were encountered in the design of the equipment, choice and handling of materials, plant operation, waste treatment, and safety and economic issues due to hazards associated with handling of lithium and ammonia and the low reaction temperature. These challenges were met, and the dissolving metal reduction chemistry was successfully implemented in two production plants for routine production.

Experimental Section

A clean dry 6000 L glass-lined reaction vessel is charged with 50 kg (0.17 kg/mol) of aziridine intermediate (**1**) and 53 kg (0.60 kg/mol) of *tert*-amyl alcohol. The reaction vessel is cooled to LT −40 °C. Using ammonia cylinders and recycled ammonia, a total of 1500 kg (2200 L) of ammonia is charged to the reactor. The reactor is set for reflux with full brine on the condenser, and the reactor contents are brought to −35 to −40 °C. Lithium is added in 200 g shots, waiting for dissolution before adding the next shot. A total of 6.2 kg (0.89 kg/mol) of lithium is added over about 2 h. The reaction mixture changes color from yellow-gray to dark blue when the reaction is complete. The reaction mixture is stirred for 30 min after the last lithium shot, and 10 L (0.56 kg/moles) of water are added in 1 kg shots while maintaining the reaction mixture at −30 to −40 °C. The color of the reaction mixture changes from dark blue to a light yellow-gray after the water addition. The ammonia is allowed to evaporate with full brine on the condenser and receiver at a pressure not exceeding 5 psig pressure in the pot. The residue on evaporation is dissolved in 1875 L of methanol, concentrated to about 150 L, and then further processed in the next step. On further processing, the free base solution was converted to the maleate salt, obtaining Sumanirole Maleate crystals that were 99.1 to 100.0 wt % pure at a combined yield of 84.2%.

Acknowledgment

The commercial process synthesis for Sumanirole Maleate (PNU-95666E), utilizing dissolving metal reduction chemistry, was developed by P. G. M. Wuts. The initial laboratory development for the dissolving metal reduction step was done in the laboratories of P. G. M. Wuts and M. A. Lyster, with the first two pilot plant lots made by M. A. Lyster. M. J. Dupuis, D. Hurley, and P. O'Driscoll supported implementation of this step in the production plants. Process safety support was provided by D. J. Knoechel and G. N. Evenson. D. J. Houser from procurement provided valuable input regarding the materials selected and facilitated sharing of technical experience from the suppliers and other contract manufacturers. The production plant and pilot plant crews at the various sites made several suggestions for equipment modifications.

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